

**FIG._1****FIG._1A****FIG._1B****FIG._1A****SEQ ID NO: 1****Nucleotide Sequence Tankyrase Homologue isotype1**

CTTTGAAGACACTGGATTTTCATACTTTTGCCTGGGGTTATCTCTCTGTGTCTCACTACATAGACAAATA
TTAGCTGTGAGCAGATCTTTTTTTGTTGCTTCTTGTAGTCCCCAGTTTAGCAGAAACATTCTGTGAGA
TAGATGTGGGAAAGGAATTCTAGCAAGAGTTTTGTCACTGTATCATAAGGTTGTGATTTACATATTTAA
GTTTTATACTTTGAACATCTGAAAATGTATACATACTAAATATGCAGAACTCTATTGTAGAGTGAGAAA
CATTTGAACTTTGAGCTTTCAGTCACTTATTTTGTATTCTTTCTTTGAGGTTAGCAGTAGTACCACCCA
AGGCACTGCTTAGGTACCACTGCTGCTTAGTGGAGAGTCCCTCTGGCTTTATCATTAAAGGTTTTGGGCG
GAAAGACGTAGTTGAATATTTGCTTCAGAATGGTGAAGTGTCCAAGCACGTGATGATGGGGGCCTTAT
TCCTCTTCATAATGCATGCTCTTTTGGTCATGCTGAAGTAGTCAATCTCCTTTTGCGACATGGTGCAGA
CCCCAATGCTCGAGATAATTGGAATTATACTCCTCTCCATGAAGCTGCAATTAAAGGAAAGATTGATGT
TTGCATTGTGCTGTTACAGCATGGAGCTGAGCCAACCATCCGAAATACAGATGGAAGGACAGCATTGGA
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CAGGAGTGGCAATGAAGAAAAAATGATGGCTCTACTCACACCATTAATGTCAACTGCCACGCAAGTGA
TGGCAGAAAGTCAACTCCATTACATTTGGCAGCAGGATATAACAGAGTAAAGATTGTACAGCTGTTACT
GCAACATGGAGCTGATGTCCATGCTAAAGATAAAGGTGATCTGGTACCATTACACAATGCCTGTTCTTA
TGGTCATTATGAAGTAACTGAACTTTTGGTCAAGCATGGTGCCTGTGTAAATGCAATGGACTTGTGGCA
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CAGAGCTGCATATTGTGGTCATCTACAAACCTGCCGCCTACTCCTGAGCTATGGGTGTGATCCTAACAT
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GTCTTTCCCTGCAGTTCAGTGCAATGAAAATGGCACATTCTCCTCCAGGTCATCACTCAGTCACTGGTAG
GCCCAGTGTAATGGCCTAGCATTAGCTGAATATGTTATTTACAGAGGAGAACAGGCTTATCCTGAGTA
TTTAATTACTTACCAGATTATGAGGCCTGAAGGTATGGTCGATGGATAAATAGTTATTTTAAGAACTA
ATTCCACTGAACCTAAAATCATCAAAGCAGCAGTGGCCTCTACGTTTTACTCCTTTGCTGAAAAAAA
AA

FIG. 1B

FIG._2**FIG._2A****FIG._2B****FIG._2A****SEQ ID NO: 2****Nucleotide Sequence Tankyrase Homologue isotype2**

CGCGCTGCTCCGCCCCCGCGGGGCGAGCCGGGGGGCAGGGAGCCCAGCGAGGGGCGCGCTGGGCGCGG
CCCATGGGACTGCGCCGGATCCGGTGACAGCAGGGAGCCAAGCGGCCCCGGGCCCTGAGCGCGTCTTCTC
CGGGGGGCGCTCGCCCTCCTGCTCGCGGGGCGGGGCTCCTGCTCCGGTTGCTGGCGCTGTTGCTGGCTG
TGGCGGCGGCCAGGATCATGTGCGGTGCGCGCTGCGCCGGCGGGGAGCGGCCTGCGCGAGCGCCGCGG
CCGAGGCCGTGGAGCCGGCCGCCGAGAGCTGTTGAGGCGTGCCGCAACGGGGACGTGGAACGAGTCA
AGAGGCTGGTGACGCTGAGAAGGTGAACAGCCGCGACACGGCGGGCAGGAAATCCACCCGCTGCACT
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ATGCAATGGACTTGTGGCAATTCCTCCTCTCATGAGGCAGCTTCTAAGAACAGGGTTGAAGTATGTT
CTCTTCTCTTAAGTTATGGTGCAGACCCAACACTGCTCAATTGTCAATAAAAGTGCTATAGACTTGG
CTCCACACCACAGTTAAAGAAAGATTAGCATATGAATTTAAAGGCCACTCGTTGCTGCAAGCTGCAC
GAGAAGCTGATGTTACTCGAATCAAAAAACATCTCTCTGGAATGGTGAATTTCAAGCATCCTCAAA
CACATGAAACAGCATTGCATTGTGCTGCTGCATCTCCATATCCCAAAGAAAGCAAATATGTGAACTGT
TGCTAAGAAAAGGAGCAAACATCAATGAAAAGACTAAAGAATTCTTGACTCCTCTGCACGTGGCATCTG
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ATCACTCAGTCACTGGTAGGCCAGTGTAATGGCCTAGCATTAGCTGAATATGTTATTTACAGAGGAG
AACAGGCTTATCCTGAGTATTTAATTACTTACCAGATTATGAGGCCTGAAGGTATGGTCGATGGATAAA
TAGTTATTTTAAGAACTAATTCCACTGAACCTAAAATCATCAAAGCAGCAGTGGCCTCTACGTTTTAC
TCCTTTGCTGAAAAAAAAAAAA

FIG._2B

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SEQ ID NO: 3**Amino Acid Sequence Tankyrase Homologue isotype1**

GFGRKDVVEYLLQNGASVQARDDGGLIPLHNACSFSGHADEVNLLLRHGADPNARDNWNYPPLHEAAIKG
KIDVCIVLLQHGAEP TIRNTDGRTALDLADPSAKAVLTGEYKKDELLESARSGNEEKMMALLTPLNVNC
HASDGRKSTPLHLAAGYNRVKIVQLLLQHGADVHAKDKGDLVPLHNACSYGHYEVT ELLVKHGACV NAM
DLWQFTPLHEAASKNRVEVCSLLSYGADPTLLNCHNKSAIDLAPTQLKERLAYEFKGHSL LQAAREA
DVTRIKKHL SLEMVNF KHPQTHETALHCAAASPYPKRKQICELL LRKGANINEKTKEFLTPLHVASEKA
HNDVVEVVVKHEAKVNALDNLGQTS LHRAAYCGHLQTCRLLSYGCDPNIIISLQGF TALQMGNE NVQQL
LQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEGRQSTPLHFAAGYNRVSVVEYLLQHG
ADVHAKDKGGLVPLHNACSYGHYEVAELLVKHGAVVN VADLWKFTPLHEAAAKGKYEICKLLLQHGADP
TKKNRDGNTPLDLVKDGD TDIQDLLRGDAALLDAAKKGCLARVKKLSSPDNVNCRDTQGRHSTPLHLAA
GYNNLEVAEYLLQHGADVNAQDKGGLIPLHNAASYGHVDVAALLIKYNACVNATDKWAFTPLHEAAQKG
RTQLCALLLAHGADPTLKNQEGQTPDLV SADDVSALLTAAMPPSALPSCYKPQVLNGVRS PGATADAL
SSGPSSPSSLSAASSLDNLSGSFSELSSVSSSGTEGASSLEKKEVPGVDF SITQFVRNLGLEHLMDIF
EREQITLDVLVEMGHKELKEIGINAYGHRHKL IKGVERLISGQQGLNPYLT LNTSGSGTILIDLSPDDK
EFQSV EEMQSTVREHRDGGHAGGI FNRYN ILKIQKVCNKKLWERYTHRRKEVSEENHNHANERMLFHG
SPFVNAI IHKGFDERHAYIGMFGAGIYFAENSSKSNQYVYIGGGTGCPVHKDRSCYI CHRQLLFCRV
TLGKSFLQFSAMKMAHSPPGHHSVTGRPSV

FIG._3

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SEQ ID NO: 4

Amino Acid Sequence Tankyrase Homologue isotype2

RCSARRGAAGGQGAQRGARVGA AHGTAPDPVTAGSQAARALSASSPGGLALLLAGPGLLLRLLALLLAV
AAARIMSGRRRCAGGGAACASAAAEAVEPAARELFEACRNGDVERVKRLVTPEKVNSRDTAGRKSTPLHF
AAGFGRKDVVEYLLQNGANVQARDDGGLIPLHNACSFSGHAEVNLLLRHGADPNARDNWNYPPLHEAAI
KGKIDVCIVLLQHGAEPTIRNTDGRTALDLADPSAKAVLTGEYKKDELLESARSGNEEKMMALLTPLNV
NCHASDGRKSTPLHLAAGYNRVKIVQLLLQHGADVHAKDKGDLVPLHNACSYGHEVTELLVKHGACVN
AMDWQFTPLHEAASKNRVEVCSLLLSYGADPTLLNCHNKSALDLAPTQPKERLAYEFKGHSLQAAAR
EADVTRIKKHLSELMVNFKHPQTHETALHCAAASPYPKRKQICELLRKANINEKTKEFLTPLHVASE
KAHNDVVEVVVKHEAKVNALDNLGQTS LHRAAYCGHLQTCRLLLSYGCDPNIISLQGF TALQMGNEVQ
QLLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEGRQSTPLHFAAGYNRVSVVEYLLQ
HGADVHAKDKGGLVPLHNACSYGHEVAELLVKHGAVVNVADLWKFTPLHEAAAKGKYEICKLLLQHGA
DPTKKNRDGNTPDLVKGDTDIQDLLRGDAALLDAKKKGCLARVKKLSSPDNVNCRDTQGRHSTPLHL
AAGYNNLEVAEYLLQHGADVNAQDKGGLIPLHNAASYGHVDVAALLIKYNACVNATDKWAFTPLHEAAQ
KGRTQLCALLLAHGADPTLKNQEGQTPDLVVSADDVSALLTAAMPPSALPSCYKPQVLNGVRS PGATAD
ALSSGPSSPSSLSAASSLDNLSGSFSELSSVSSSGTEGASSLEKKEVPGVDF SITQFVRNLGLEHLMD
IFEREQITLDVLVEMGHKELKEIGINAYGHRHKLKIGVERLISGQQLNPYLT LNTSGSGTILIDLSPD
DKEFQSV EEMQSTVREHRDGGHAGGIFNRYNLIKIQVCNKKLWERYTHRRKEVSEENHNHANERMLF
HGSPFVNAI IHKGFDERHAYIGGMFGAGIYFAENSSKSNQYVYGIGGGTGCPVHKDRSCYICHRQLLFC
RVTLGKSFLQFSAMKMAHSPPGHHSVTGRPSVNGLALAEYVIYRGEQAYPEYLITYQIMRPEGMVDG

FIG. 4

Schematic Presentation of Dominant Negative Mutants for Tankyrase Homologue

Dominant Negative Mutants

Truncation: 429 Δ C- of the C-terminal catalytic domain – truncation of the catalytic domain of PARP acts as a dominant negative when overexpressed *in vivo* (Oncogene 1999 Nov 25; 18(50):7010-5)

Point mutant: E945A Δ C- conserved residue in PARP domain, thought to be important in NAD⁺ binding

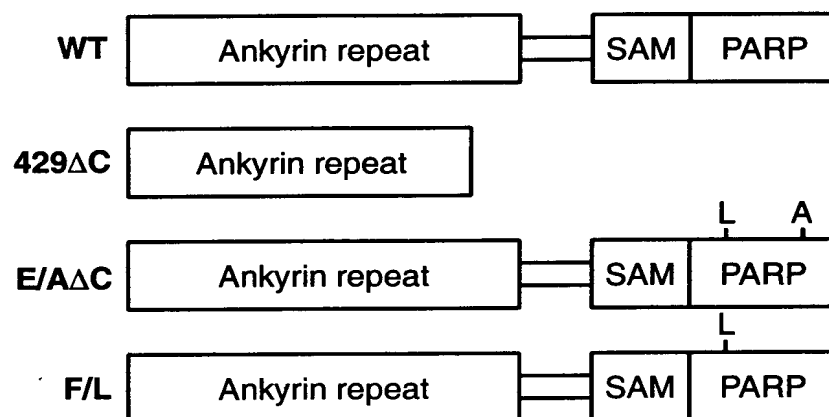


FIG._5

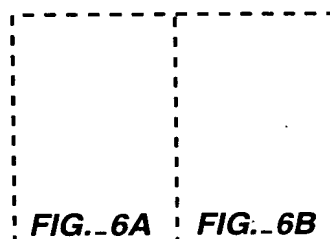


FIG._6

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**Cell Cycle Analysis of A549 Cells
Infected With GFP-fused Wild Type
and Mutant Tankyrase Homologue**

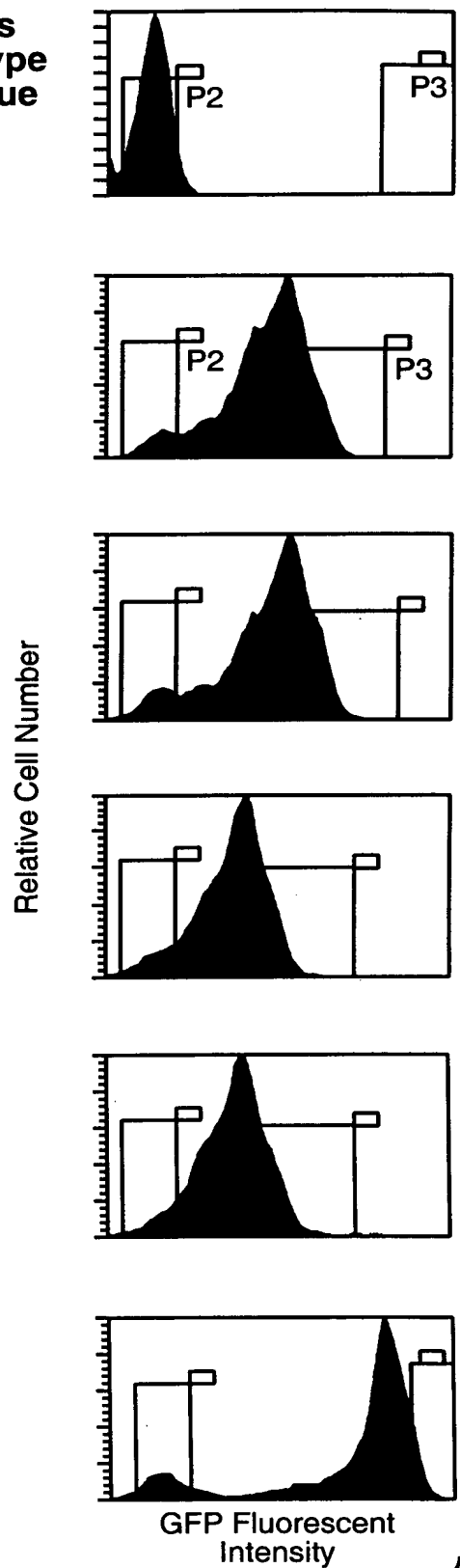
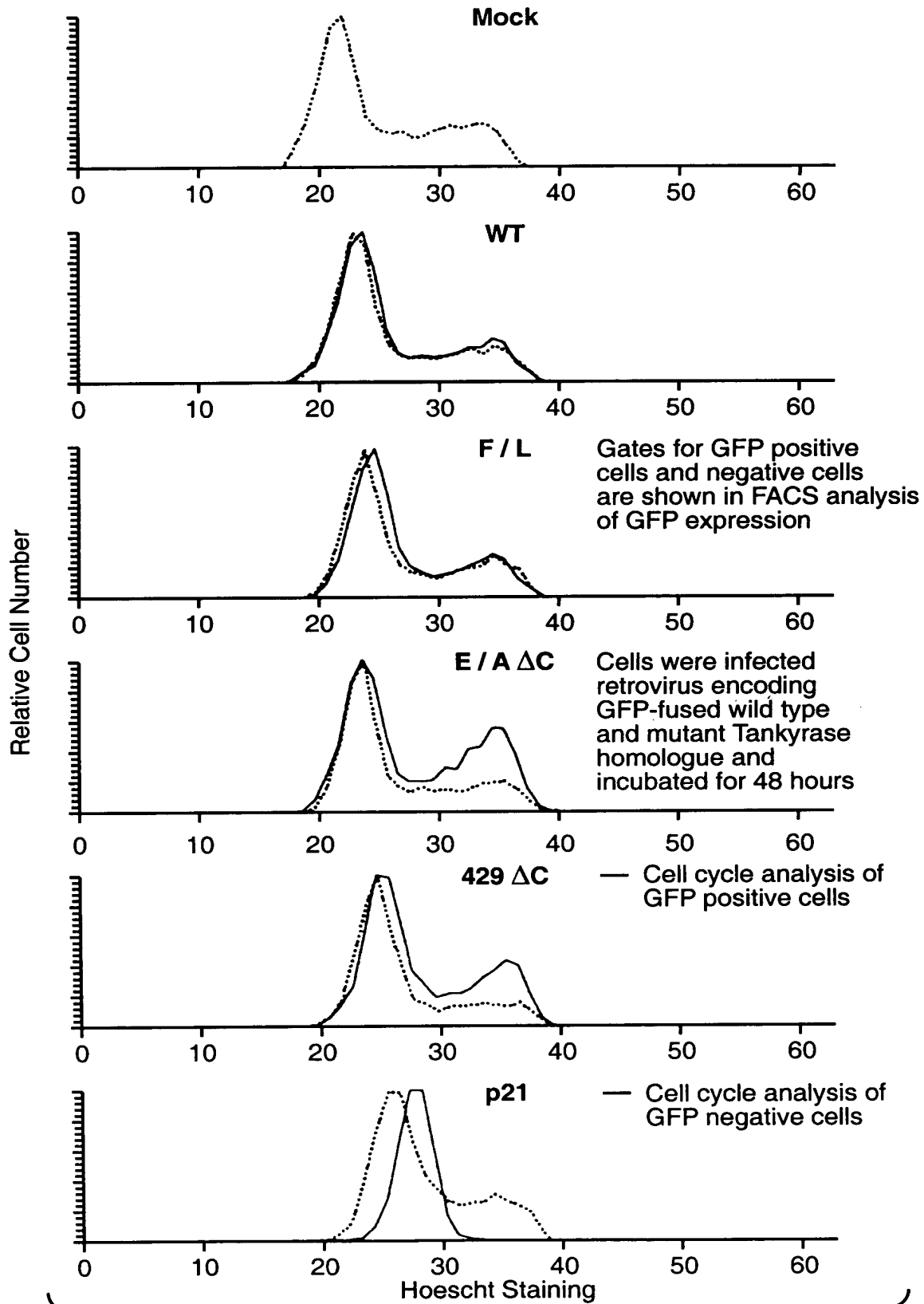


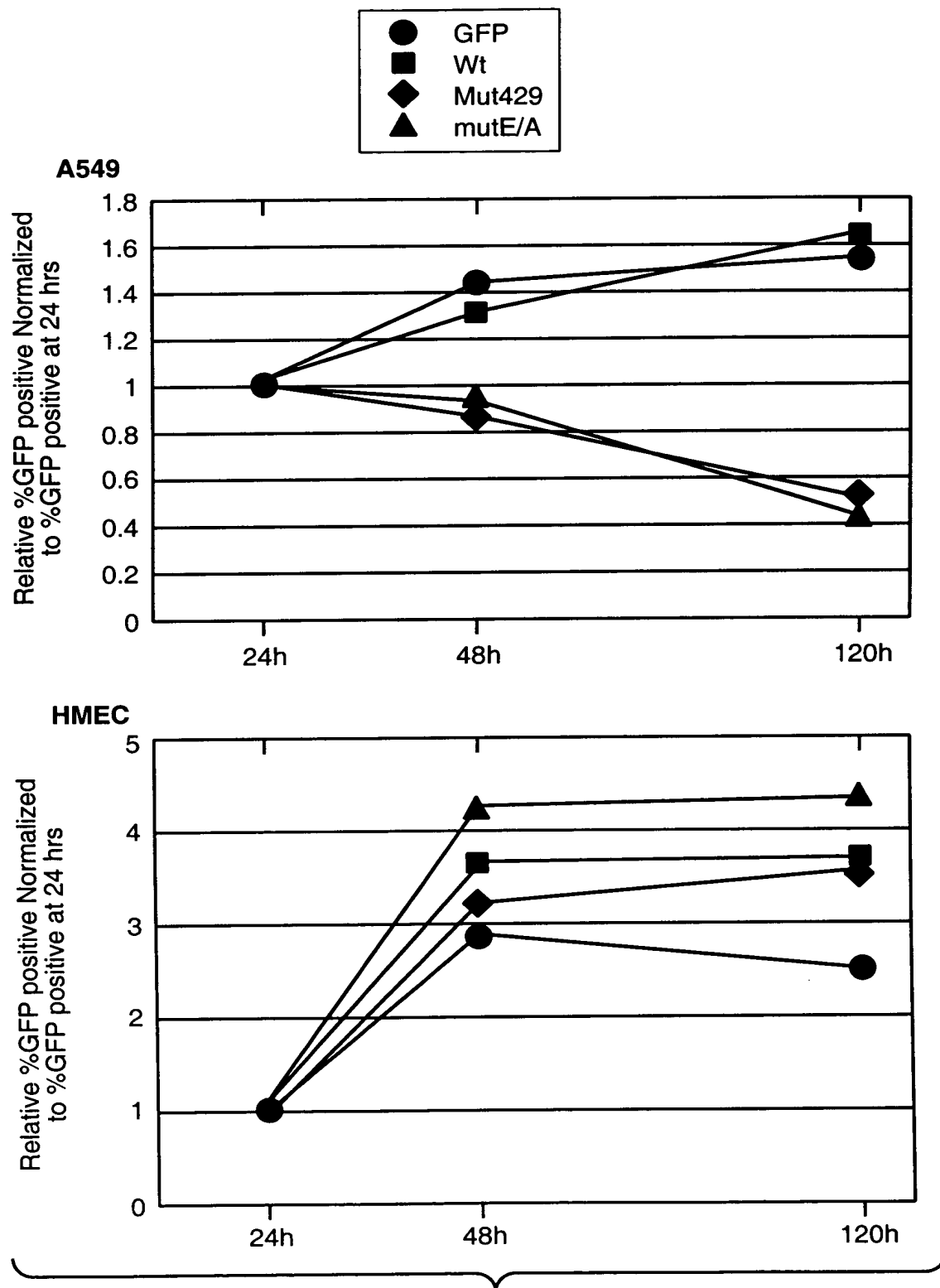
FIG. 6A

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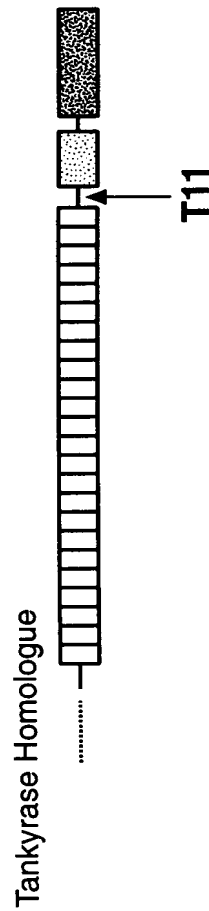
**FIG. 6B**

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Kinetics of GFP Positive cells in A549 Cells and Human Mammary Epithelial Cells (HMEC) After Retrovirus Infection Encoding GFP-fused Wild Type and Mutant Tankyrase Homologue

**FIG. 7**

The Binding Site of Antisense Oligos Against Tankyrase Homologue



Ankyrin repeat
 SAM
 PARP

..... Unidentified sequence



T11

	GTGGAACACAGAGGGTGCTTCC	
Tankyrase Homologue	GTGGAACACAGAGGGTGCTTCCAGTTTGGAGAAAAGGAGGTTCCAGGAGTAGATTTTAGCAT	2838
Tankyrase	ATGCAGGGGATGGCGCCGCGGGAACAGAAAAGGAAGGAGAAAGTTGCTGGTCTTGACAT	3091
	** *	

FIG._8

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Anti-Proliferative Phenotype of Antisense Oligonucleotides Against Tankyrase Homologue in A549 and HeLa Cells

 T11-SCR
 T11

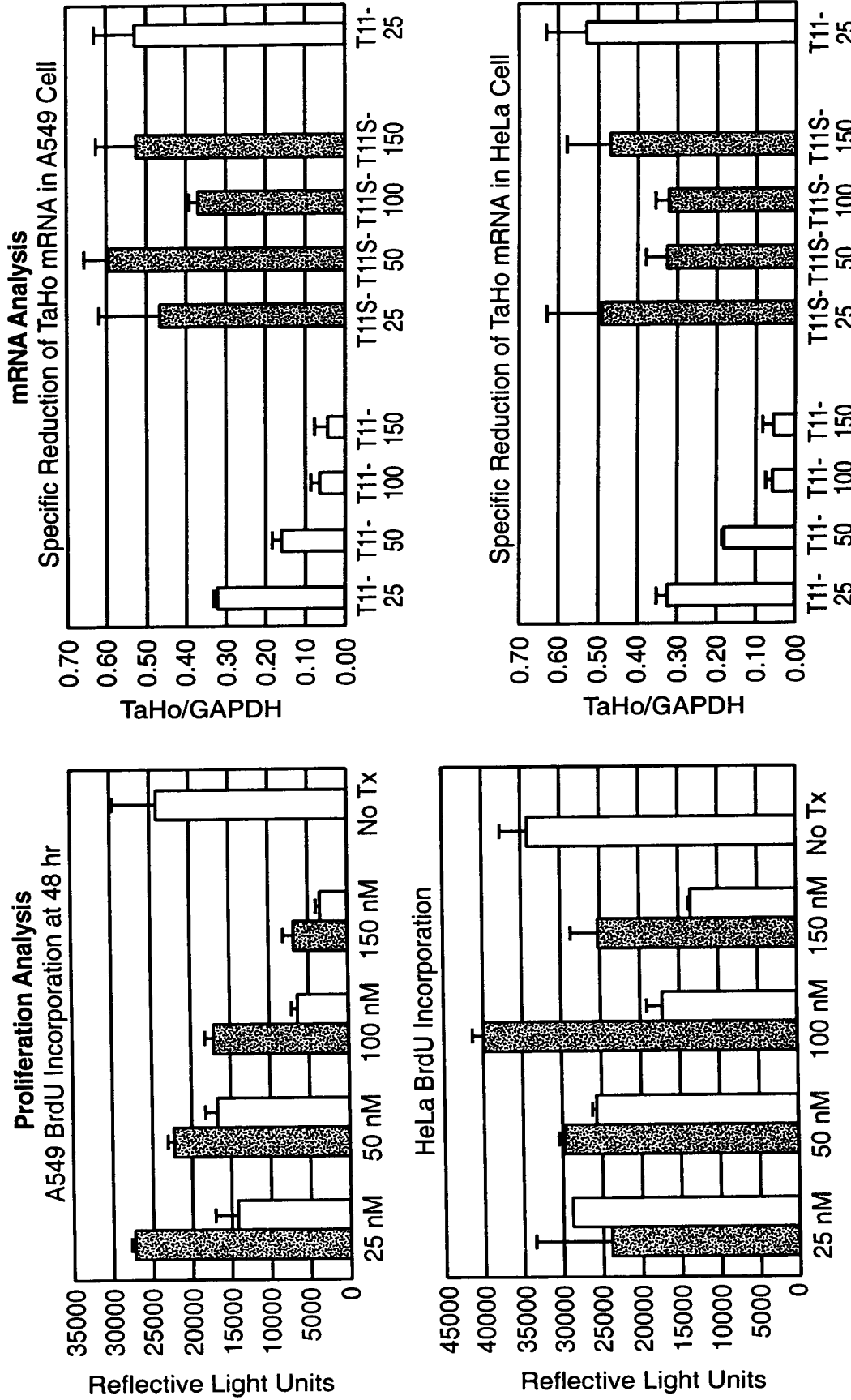
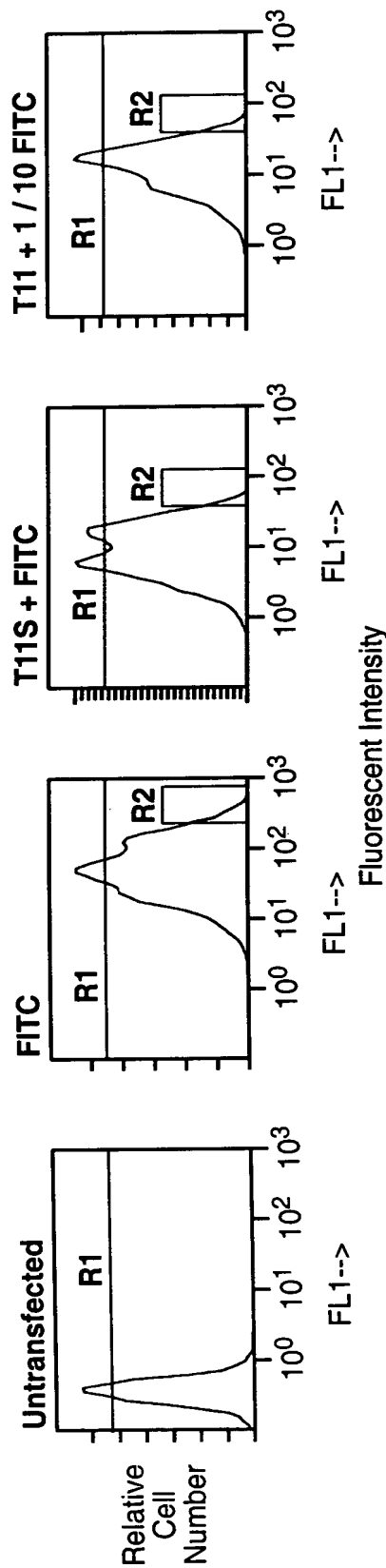


FIG._9

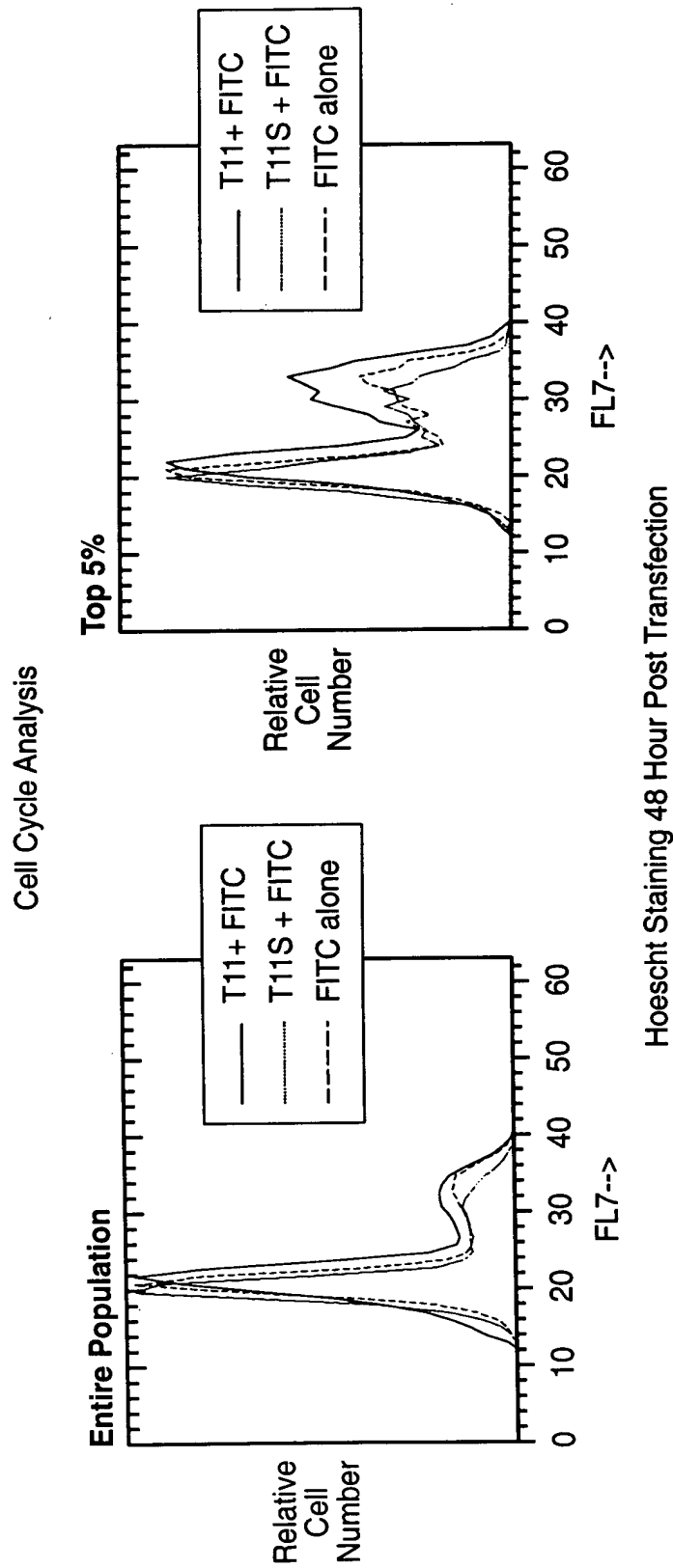
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Cell Cycle Analysis of A549 Cells Transfected with Antisense Oligonucleotides Against Tankyrase Homologue at 48 Hours, Antisense Oligonucleotides (T11) and Control Oligonucleotides (T11S) were transfected with FITC-labeled random 20mer Oligonucleotides (FITC), After 48 Hours, entire population (R1) and Top 5% (R2) of FITC transfected cells were analyzed for cell cycle

Gates for Cell Cycle Analysis

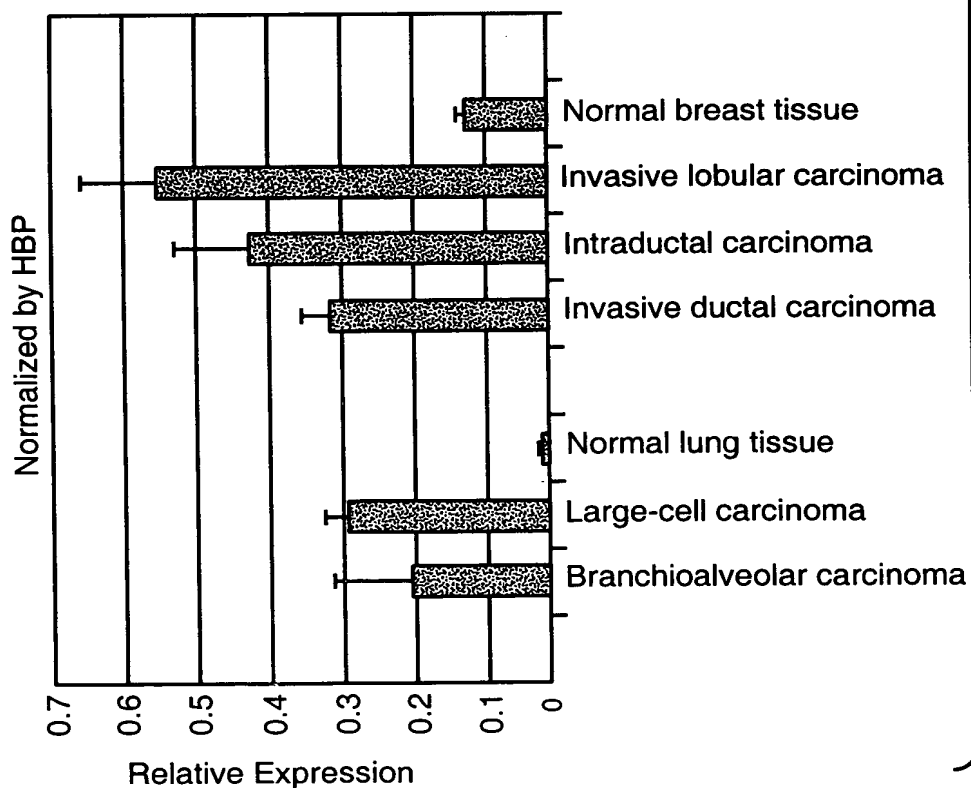
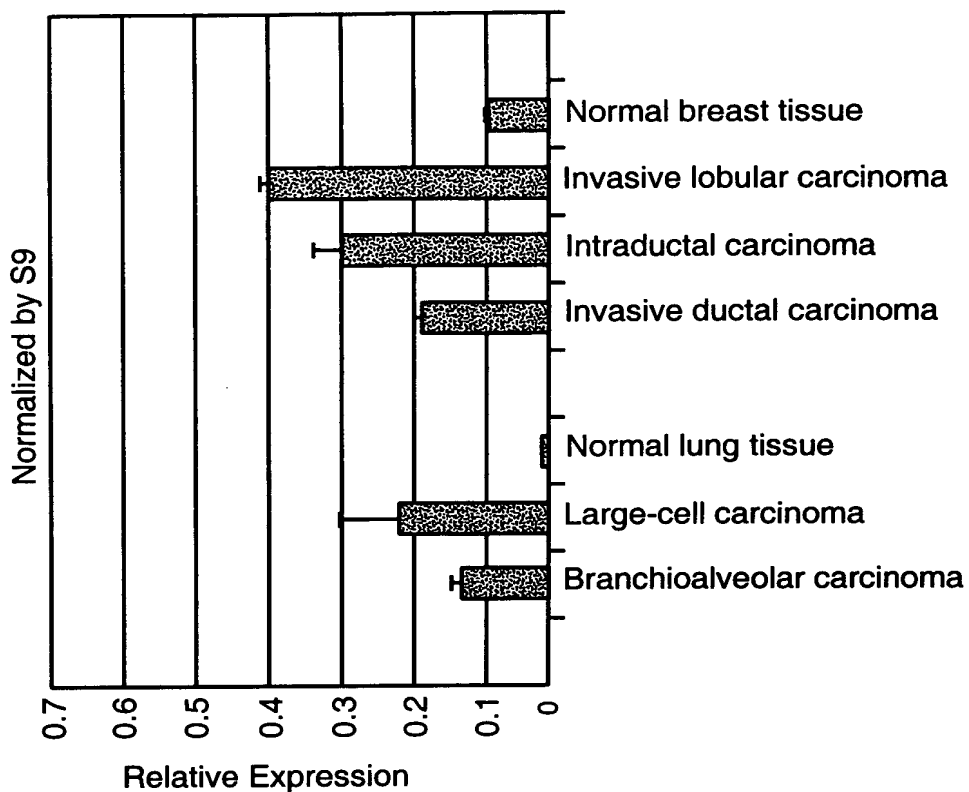
**FIG.. 10A**

Cell Cycle Analysis of A549 Cells Transfected with Antisense Oligonucleotides Against Tankyrase Homologue at 48 Hours, Antisense Oligonucleotides (T11) and Control Oligonucleotides (T11S) were transfected with FITC-labeled random 20mer Oligonucleotides (FITC), After 48 Hours, entire population (R1) and Top 5% (R2) of FITC transfected cells were analyzed for cell cycle

**FIG. 10B**

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mRNA Expression of Tankyrase Homologue in Several Tumors and Normal Tissues by a Taqman Analysis, mRNA Expression was Normalized by 90kDa Highly Basic Protein (HBP) and Ribosomal Protein S9 (S9)

**FIG. 11**

**Procedure for Nonisotopic Detection of Poly-ADP Ribosylation
Using Anti-GFP mAb-Coated Plates**

Protein lysates from 293T cells normalized by GFP
fluorescence and total protein

Immobilization of GFP-tankyrase homologue in anti-
GFP Coated plates

Auto PARP reaction with Biotinylated-NAD in 96 wells

Detection of poly ADP ribose chains with Streptavidin-
HRP and chemiluminescent substrate

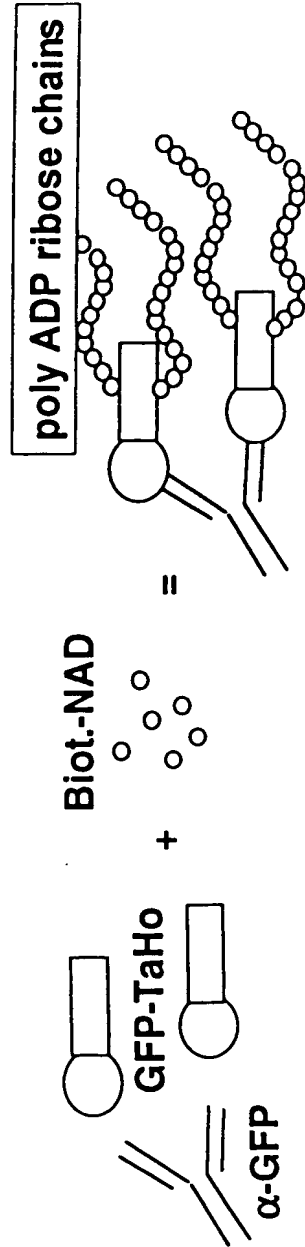
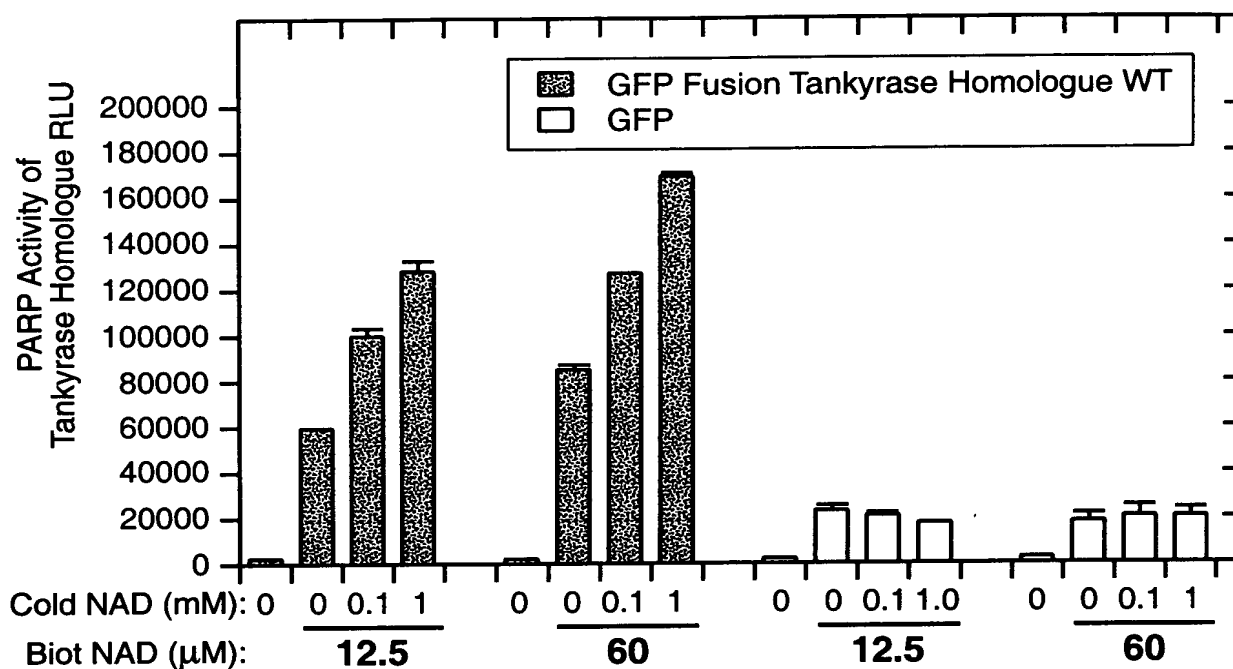


FIG._12

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Non-Isotopic Plate-Based Detection of TaHo PARP Activity in the Presence of Biotinylated NAD

**FIG. 13**

Comparison of IC₅₀ Values of the PARP Inhibitors

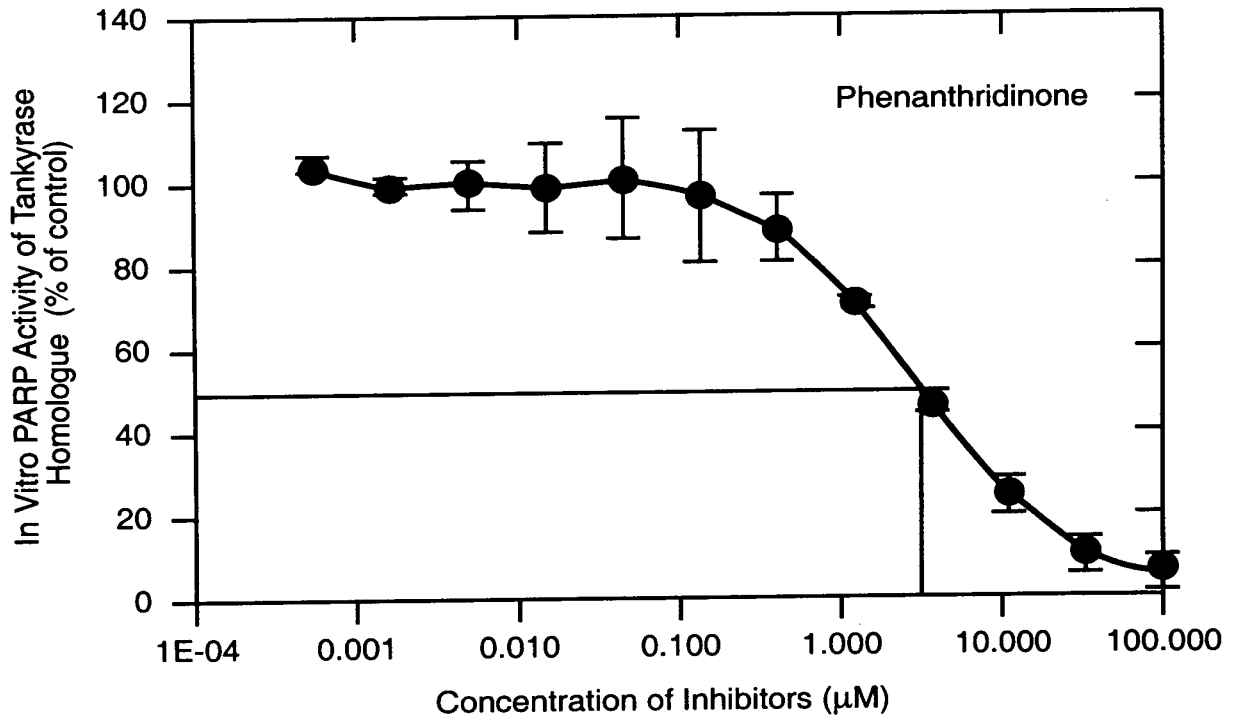
	Approximate IC ₅₀ (nM)	hPARP assay IC ₅₀ (nM)		
	TaHo	Rigel	Decker*	Rankin*
3AB	>50 000	5 000	2 000	5 400
6(5H)Phenanthridinone	1 000-2 000	300		
Niacinamide	>50 000	30 000	>>5 000	31 000

* Decker P et al., Clinical Cancer Research. 1999 May; 5:1169-1172

* Rankin PW et al., J Biol Chem. 1989 Mar 15;264(8):4312-4317

FIG. 14

Inhibition of Tankyrase Homologue PARP Activity by hPARP Inhibitors

**FIG._15****FIG._16****FIG._16A****FIG._16B****FIG._16C**

TH-1: Tankyrase Homologue isoform-1, TH-2: Tankyrase Homologue isoform-2 **FIG. 16A**
M (Red): the first methionine in the sequence, Z: stop codon
In this figure, the first methionine in TH-1 sequence is position 1 (M1)

Taho C terminus deletion mutant ends at position 429 (K) and adds 28 amino acids because of frame shift.

Taho F/L mutant has the mutation at position 871

Taho E/A dC mutant has the mutation at position 948, ends at position 957 (A) and adds 2 amino acids.

TH-1	-----	RCSARRGAAGGQGAQRGARVGAAGHTAPDPVTAGSQ	-231
TH-2	-----		
TH-1	-----	AARALSASSPGGLALLAGPGLLLRLALLLAVAAARIMSGRRRCAGGGAACASAAAEAVE	-171
TH-2	-----		
TH-1	-----	-----*GFGRKDVVEYLLQNGA	-111
TH-2	-----	PAARELFEACRNGDVERVKRLVTPEKVNSRDTAGRKSTPLHFAAGFGRKDVVEYLLQNGA	-111
	Ankyrin repeat	Ankyrin repeat	
TH-1	SVQARDDGGLIPLHNACSEFGHAEVVNLLLRHGADPNARDNWNNTPLHEAAIKGKIDVCIV		-51
TH-2	NVQARDDGGLIPLHNACSEFGHAEVVNLLLRHGADPNARDNWNNTPLHEAAIKGKIDVCIV		-51
	Ankyrin repeat	Ankyrin repeat	
		•TH1 start	
TH-1	LLQHGAETIRNTDGR TALDLADPSAKAVLTGEYKKDELLESARSNGNEEKMALLTPLNV		10
TH-2	LLQHGAETIRNTDGR TALDLADPSAKAVLTGEYKKDELLESARSNGNEEKMALLTPLNV		10

FIG. 16B

	Ankyrin repeat	Ankyrin repeat
TH-1	NCHASDGRKSTPLHLAAGYNRVKIVQLLLQHGADVHAKDKGDLVPLHNACSYGHYEVT	70
TH-2	NCHASDGRKSTPLHLAAGYNRVKIVQLLLQHGADVHAKDKGDLVPLHNACSYGHYEVT	70
	Ankyrin repeat	Ankyrin repeat
TH-1	LVKHGACVNA MDLWQFTPLHEAASKNRVEVCSLLLSYGADPTLLNCHNKSAIDLAPTQL	130
TH-2	LV	
	Ankyrin repeat	
TH-1	KERLAYEFKGHSLQLQAAREADVTRIKKHLSELMVNFKHPQTHETALHCAAASPYPKRKQI	190
	Ankyrin repeat	Ankyrin repeat
TH-1	CELLLRKGANINEKTEFLTPLHVASEKAHNDVVEVVVKHEAKVNALDNLGQTSLHRAAY	250
	Ankyrin repeat	
TH-1	CGHLQTCRLLLSYGCDPNIISLQGF TALQMGNEVQQLQEGISLGNSEADRQLLEAACA	310
	Ankyrin repeat	Ankyrin repeat
TH-1	GDVETVKKLCTVQSVNCRDIEGRQSTPLHFAAGYNRVSVVEYLLQHGADVHAKDKGGLVP	370
	Ankyrin repeat	Ankyrin repeat
TH-1	LHNACSYGHYEVAELLVKHGAVNVADLWKFTPLHEAAAKGYEICKLLQLQHGADPTKKN	430
	Ankyrin repeat	Ankyrin repeat
		Deletion--
TH-1	GMEILLWILLKMEIQIFKICLGEMQLCZ	
	RDGNTPLDLVKDGDTDIQDLLRGDAALLDAAKGCCLARVKLSSPDNVNCRDTQGRHSTP	490
	Ankyrin repeat	

FIG. 16C

TH-1	LHLAAGYNNLEVAEYLLQHGADVNAQDKGLIPLHNAASYGHVDVAALLIKYNACVNATD 550
	<div style="display: flex; justify-content: space-between;"> <div>Ankyrin repeat</div> <div>Ankyrin repeat</div> </div>
TH-1	KWAFTPLHEAAQKGRQTQCALLLAHGADPTLKNQEGQTPLDLVSADDVSALLTAAMPSPA 610
	<div style="display: flex; justify-content: space-between;"> <div>Ankyrin repeat</div> <div>Ankyrin repeat</div> </div>
TH-1	LPSCYKPQVLNGVRSPGATADALSSGPPSSLSAASSLDNLSGSFSELSSVSSSGTEG 670
	<div style="display: flex; justify-content: space-between;"> <div>Ankyrin repeat</div> <div>Ankyrin repeat</div> </div>
TH-1	ASSLEKKE--VPGVDFSITQFVRNLGLEHLMIDIFEREQITLDVLVEMGHKELKEIGINAY 730
	<div style="display: flex; justify-content: space-between;"> <div>SAM domain</div> <div></div> </div>
TH-1	GHRHKLIGVERLISGQQLNPYLTNTSGSGTILIDLSPDDKEFQSVEEEMQSTVREHR 790
TH-1	DGGHAGGIFNRYNIIKIQVCNKKLWERYTHRRKEVSEENHNHANERMLFHGSPFVNAIL 850
TH-1	HKGFDERHAYIGGMFGAGIYFAENSSKSNQYVYIGGGTGPCVHKDRSCYICHRQLLFCR 910
	<div style="display: flex; justify-content: space-between;"> <div>• F→L mutation</div> <div>PARP domain</div> </div>
TH-1	VTLGKSFLQFSAMKMAHSPPGHHSVTGRPSVNGLALAEYVIYRGEQAYPEYLITYQIMRP 970
	<div style="display: flex; justify-content: space-between;"> <div>•E→A</div> <div>•Deletion.</div> </div>
TH-1	EGMVDG 976

-----A-----LSZ